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Dyspnea: Diagnostic and Therapeutic Implications

EDWARD A. GAENSLER

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EDWARD A. GAENSLER

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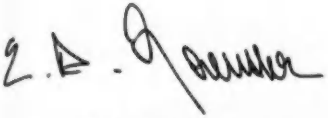

is Associate Professor of Surgery and Director of the Thoracic Services at the Boston University-Massachusetts Memorial Hospitals Medical Center. He received his B.S. from Haverford College and his M.D. from Harvard Medical School. He served residencies in general and thoracic surgery at the Boston City Hospital. This prompted interest in applied pulmonary physiology. Work in this field has continued since 1947 first as U.S.P.H.S. Research Fellow, then in the Air Force and later as Edward Livingston Trudeau Fellow with the Thorndike Memorial Laboratory and the Departments of Medicine and Surgery at Harvard Medical School.

> "Nowhere in medicine, perhaps, does the patient, whole and entire, so much need to be considered as in the field of respiration. Breathing is truly a strange phenomenon of life, caught midway between the conscious and the unconscious, and peculiarly sensitive to both."
>
> DICKINSON W. RICHARDS, JR. (30)

DYSPNEA is a subjective symptom. The patient first must be aware of a sensation and then he must express an opinion that this sensation is abnormal, unpleasant, frightening or limiting his activity. Both awareness and opinion are influenced, in part, by factors wholly unrelated to the presence or the severity of organic disease. Language, or difficulty of communication, is only one of many such variables. Other factors which may modify the patient's awareness or opinion are ability to observe and judge, the degree of intelligence and training, the judgment of co-workers and relatives and, most important, his preoccupation with health and well-being—his reaction to unaccustomed or

unpleasant bodily sensations. In this regard, dyspnea has been compared to pain: some patients have little pain but suffer much, while others may have severe pain but suffer little (9). Other variables are the patient's opinion concerning what constitutes normal limitation as the result of advancing age, the severity of physical work required by daily tasks both occupational and recreational and the vigor, speed and efficiency with which these tasks are customarily performed. In this connection the difference between disability and impairment cannot be overemphasized. A coal miner or professional football player may be greatly disabled by relatively little pulmonary or cardiac impairment, while a draftsman or housewife may complain of little disability despite severe impairment. It is because of such modifying factors that subjective dyspnea never correlates perfectly with the results of objective functional tests (see Figs. 1 and 2), nor will a linear relationship ever be found even if an absolutely standard stress could be devised.

The term "objective dyspnea" should be avoided. Dyspnea is a subjective sensation or symptom and as such cannot be observed by others. A number of suitable terms, including tachypnea, polypnea, hyperpnea, oligopnea or their English counterparts, can be used for objective description. Furthermore, "objective dyspnea" implies that all factors in the causation of the sensation of dyspnea have been identified or can be related to objective measurements; this is not the case.

Terms such as "dyspnea index"* (33, 36) and "breathing reserve"* (2) which relate ventilatory requirement to breathing capacity during a stated activity are useful largely in a statistical sense. In other words, it is true that the vast majority of patients with a ventilatory requirement of more than 50% of their maximal breathing capacity (MBC)* during a given exercise (dyspnea index more than 50%) complain of shortness of breath, while nearly all who have a dyspnea index of less than 35% do not. Yet, there are many exceptions: some patients with severe emphysema and a dyspnea index of 60–80% do not complain, perhaps because they are accustomed to the sensation or perhaps because their intrathoracic pressure-air flow relationships are not

*See List of Abbreviations, following the text.

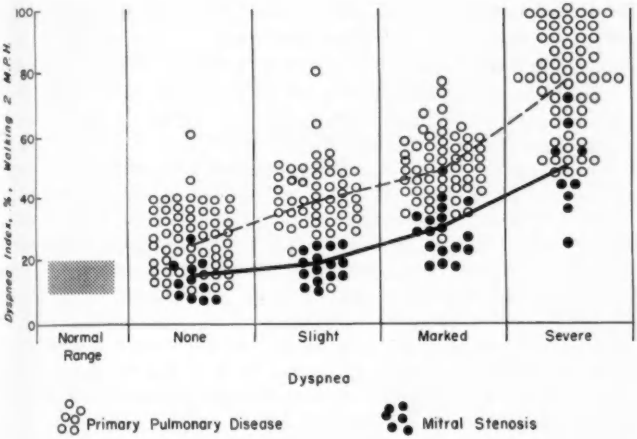

FIG. 1.—Exercise dyspnea index (minute ventilation × 100/maximal breathing capacity) of 216 patients with pulmonary impairment due to primary pulmonary disease and 53 patients with mitral stenosis correlated with subjective dyspnea while walking on the level at the rate of 2 mph.

the same during the MBC test as during exercise. Others, particularly those with fixed low cardiac output, complain of "shortness of breath" while the dyspnea index is considerably less than 35% (Fig. 1). "Dyspnea" here often implies an inability to continue with exercise because of fatigue, muscle ache, discomfort or general weariness. All these sensations together, or the inability to go on, patients have learned to call "shortness of breath" because the symptom concerning which they have been questioned by their physicians since the day the apical diastolic murmur was first discovered was called by that name.

"Shortness of breath" is a summary term for a variety of sensations which the patient considers abnormal. Aside from the subjective variables described above, there are almost certainly different kinds of "shortness of breath," depending upon the origin of the sensation and the type of impairment.

The most common sensation leading to the complaint of dyspnea is probably the impression that excessive work is required for breathing. In this regard, the sensation of the patient with airway obstruction may be somewhat akin to that of the normal subject after climbing five or six flights of stairs. Yet, even under two conditions requiring a similar increase in work of breathing, there may be great differences both physiologic and psychologic. The tremendous work of breathing of the performing athlete, associated with voluminous ventilation, may be accepted as normal, or can be an exhilarating experience; arterial blood and tissue oxygenation is normal and there may even be overbreathing and respiratory alkalosis. In contrast, the agonizing fight for every breath, the exhausting work of breathing of the patient with far-advanced chronic obstructive emphysema may result in little ventilation and is associated with hypoxia and hypercapnia. It must be an entirely different and unacceptable sensation, albeit, also one associated with greatly increased work of breathing.

The "dyspnea" associated with underventilation due to respiratory muscle paralysis is a feeling of suffocation associated with abnormally small, rather than excessive, work of breathing. It may be akin to the experience of the normal subject near the end of prolonged breath-holding. The unpleasant sensation probably is due partly to the unaccustomed immobility of the chest wall and partly to acute respiratory acidosis. It is quite different from the "dyspnea" which is the consequence of excessive work of breathing.

One might well ask whether or not a normal person ever experiences exactly the same sensation that dyspneic patients complain of. The breathlessness of the patient is usually associated with other unpleasant physical sensations or mental associations. Chest pain, muscle cramps, fatigue, dizziness, fever or chills all may be admixed to varying degrees with breathlessness. With coronary occlusion, pulmonary embolism, pneumonia or chest injuries, the other sensations may so predominate and distract that there may be no awareness of shortness of breath despite severe pulmonary impairment. The same degree of pulmonary abnormality may lead to varying complaints, depending upon associated surprise, fright, realization of progression of

disease, fear of inability to continue with work and so on. These associated sensations cannot be reproduced in a normal subject even though breathlessness can be produced temporarily by chest-binding, CO_2 inhalation, airway obstruction, etc.

EXPERIMENTAL WORK

Our knowledge concerning dyspnea has been reviewed every decade during the last half century (6, 25, 29, 30). These reviews have largely dealt with the pathophysiology of specific types of dyspnea. Experimental studies dealing with the sensation of dyspnea itself are few indeed, in part, because the only suitable subject for study is man and, in part, because of the impossibility of recording either the quality or the quantity of the sensation resulting from the experimentally applied stimulus. Our ignorance concerning the neuroanatomic basis of the awareness of respiratory distress has been summarized recently (9).

It is thought that dyspnea is experienced as the result of accumulating metabolic products when the work of the respiratory muscles becomes great in relation to the flow of oxygenated blood through them. This mechanism may apply in normal persons during exercise and in patients with abnormally increased work of breathing, low cardiac output syndromes and anemia. It cannot explain the "dyspnea" during breath-holding and that which occurs with respiratory muscular failure. Concerning this, several interesting experiments and observations have been made recently which suggest that the reduced mobility of the lungs or the chest wall, or both, may lead to a sensation of "smothering" which is not directly related to hypoxemia or hypercapnia.

Tight taping or binding of the entire chest and abdomen in the pulmonary resting position has relatively little effect on the MBC, yet during mild exercise it causes intense respiratory discomfort (35). Or, if a normal subject uses a spirometer which is electrically controlled so that he can breathe only with tidal volume and at a respiratory rate which he previously used while at rest, an intense air hunger soon develops. However, if the control mechanism is interrupted every 2 or 3 minutes to permit a sigh, the subject can breathe with this "smothering machine" indefinitely. Interestingly, a deep breath of N_2 or even of 7.4% CO_2 produced the same sense of relief as a breath of air (35). Several

other related observations have been made: *(1)* conscious subjects who have received curare to the point of complete respiratory paralysis develop intense air hunger despite the fact that they are receiving perfectly adequate alveolar ventilation by pressure breathing (31); *(2)* high spinal anesthesia may cause dyspnea when thoracic sensation is lost but respiratory muscle activity is unimpaired (9), and *(3)* paralyzed patients in a respirator may develop dyspnea which disappears if the machine is adjusted to produce an occasional deeper inspiration. Subjects who have held their breath to the breaking point can continue for a while longer (after brief rebreathing into a bag) even though the gas in the bag contains no O_2 and a higher CO_2 concentration than that in the alveolar gas (15, 35). Indeed, it can be shown that restriction of the volume of gas in the lungs is an independent ventilatory stimulus which relates to the sensation of "smothering" (26).

These experiments concerning the sensation of breathlessness are reminiscent of those of Breuer and later of Head concerning the effect of lung inflation upon the breathing pattern. It has been speculated that when the activity of the inspiratory cells in the respiratory center is so great that it cannot be neutralized by afferent stretch impulses from the lung, the inspiratory cells may continue to send out impulses throughout the entire respiratory cycle with a consequent sensation of breathlessness. Similarly, very weak impulses from the stretch receptors within the lungs, the thorax, or both, may fail to neutralize the inspiratory impulses and the persistence of the inspiratory discharge throughout respiration may cause a sensation of dyspnea. The act of taking a deep breath may thus bring relief from dyspnea not only because of readjustments of blood gas tension but also because of stretch of the lung (35).

There are almost no published observations concerning the reaction of different individuals in differing circumstances to the same degree of pulmonary impairment. We have obtained some evidence that a patient who has a constantly increased work of breathing and is used to the sensation is much more tolerant of an increment in the work of breathing than is a normal subject or a patient with intermittent breathlessness. A breathing circuit was constructed in which a resistance in the form of a photographic iris diaphragm could be varied without the patient's

knowledge. Normal subjects and asthmatics during a free interval invariably noted a sensation of labored breathing or obstruction when the diameter of the diaphragm was reduced to 18 or 20 mm. In contrast, patients with severe obstructive emphysema did not notice, or perhaps did not complain of, an alteration in their breathing until the diameter was reduced to 14 or 10 mm. The emotional response to respiratory obstruction is well illustrated by the common observation that patients who must breathe through a tracheostomy tube do not tolerate obstruction of this orifice by others even for an instant. Yet, they are able to hold a finger over the opening for as long as half a minute without reacting unfavorably.

CLASSIFICATION OF CAUSES OF DYSPNEA

The following outline of the various disorders which may lead to an awareness of respiratory distress is presented with some trepidation. The listing is incomplete. Also, nearly always in cardiopulmonary disease, dyspnea results from a combination of several of the factors mentioned. Furthermore, enumeration of a number of abnormalities of function commonly associated with dyspnea does not imply that the neuroanatomic connections between cause and effect are understood.

I. Abnormally increased work of breathing because of decreased breathing capacity
   A. Restrictive ventilatory impairment
      1. Decreased compliance* of the thorax
         (Kyphoscoliosis; ankylosing spondylitis; thoracoplasty)
      2. Decreased compliance of the lung
         (Pulmonary fibrosis; reduction in functioning lung; pleural, mediastinal or abdominal displacement of lung; pulmonary edema; rapid breathing with chronic obstructive emphysema; heart disease; ? old age)

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*"Compliance" is an expression of the elastic properties of an object. It relates the amount of "stretch" to the unit of force which is applied. In the case of the lungs and thorax, the "stretch" is measured in terms of volume change, and the force is measured in terms of pressure applied to the system. The normal compliance of the lungs is about 0.2 L./cm. of H_2O and that of the lungs and thorax together about one-half that much.

B. Obstructive ventilatory impairment
   1. Increased airway resistance
      (Local: vocal chord lesions or paralysis; major airway compression or tumor. Diffuse: chronic obstructive emphysema; bronchial asthma; ? chronic bronchitis; ? cigaret smoking; heart disease)
   2. Increased resistance of tissues to deformation (increased tissue viscous resistance)
      (Pulmonary fibroses and granulomatoses; kyphoscoliosis; bronchial asthma; heart disease)

II. Abnormally increased work of breathing because of increased ventilatory requirement
   A. Metabolically justified hyperventilation: ratio of ventilation to O_2 uptake normal
      (Hyperthyroidism, fever, exercise)
   B. Metabolically unjustified hyperventilation: ratio of ventilation to O_2 uptake increased
      1. Increased dead space
         a) Increased effect of anatomic dead space: shallow breathing
            (Chest pain; pulmonary fibrosis; edema; embolism)
         b) Increased physiologic dead space: ventilation of poorly perfused or unperfused alveoli
            (Pulmonary embolism; absence of pulmonary artery; chronic obstructive emphysema; most other cardiopulmonary diseases)
      2. Hypoxemia
         a) Due to alveolar underventilation
            (Decompensated restrictive or obstructive insufficiency; high altitude; mining accidents)
         b) Due to venous-arterial shunt
            i) Cardiovascular anomalies
            ii) "Lung shunts": perfusion of poorly ventilated or unventilated alveoli
               (Atelectasis; pulmonary edema; chronic obstructive emphysema; bronchial asthma; most other cardiopulmonary diseases)
         c) Due to decreased diffusing capacity of the pulmonary membrane

("Alveolar-capillary block" in pulmonary granulomatoses, fibroses, other diffuse lung disease; decrease in size of membrane; resection; chronic obstructive emphysema)

3. Reflexly stimulated hyperventilation
   a) By stretch receptors of lungs and thorax
   (Pulmonary fibrosis; granuloma; chest deformity)
   b) By vascular receptors in pulmonary vessels
   (Pulmonary hypertension)
4. Hyperventilation due to acidosis
   (Metabolic or renal acidosis; drugs)
5. Increased sensitivity of respiratory center to CO_2
   (Chronic hypoxemia; progesterone; salicylates; convulsants: coramine, picrotoxin; ? fever)
6. Cortically stimulated hyperventilation
   a) Usually with "dyspnea," "dizzy spells," "inability to take deep breath"
   (Hyperventilation syndromes; psychoneuroses; Da Costa's syndrome; effort syndrome)
   b) Usually not associated with dyspnea
   (Encephalitis; cerebral vascular accidents; hysteria; severe pain; sexual and other excitement)

III. Dyspnea not associated with increased work of breathing

A. Respiratory muscle insufficiency
   1. Central nervous (bulbar poliomyelitis; cerebral vascular accidents; drugs)
   2. Nervous pathways (spinal poliomyelitis)
   3. Muscle itself (old age; myasthenia gravis; porphyria)

B. Tissue hypoxia due to circulatory impairment
   1. May not be associated with significant lung disease
   (Pulmonic stenosis, etc.)
   2. Usually associated with significant secondary lung disease
   (Low output failure; mitral stenosis, etc.)

C. Tissue hypoxia due to decreased oxygen capacity of the blood (may or may not be associated with dyspnea)
   (Anemia; methemoglobinemia; carbon monoxide poisoning)

IV. Dyspnea of unexplained origin
   A. Without demonstrable organic disease and without hyperventilation
      (Organic disease present but not detected ?; faulty communication with patient; poor judgment of patient; very rarely, malingering)
   B. Dyspnea of pulmonary hypertension with well maintained cardiac output
   C. Dyspnea of various muscular paralytic states in presence of adequate alveolar ventilation
      (Respirator patients; dyspnea with curare or spinal anesthesia)

Obviously, a unitarian explanation for the symptom of dyspnea is not possible, much as the control of respiration cannot be explained by a single factor. Most studies concerned with the origin of dyspnea have centered on correlating this symptom with an objectively measurable quantity, such as breathing capacity, dyspnea index or arterial blood gases. Inasmuch as in the vast majority of situations leading to dyspnea the work of breathing is increased (Groups I and II above), and inasmuch as these conditions are perhaps best understood, a brief consideration of the factors involved in the work of breathing may be appropriate.

THE WORK OF BREATHING

In general, two different kinds of work are required for the act of breathing. One is necessary to overcome the elastic recoil of the lungs and thorax and is proportional to the distance, or here the volume, by which lungs and thorax have been moved. The other work is that required to overcome resistance to movement and is proportional to the speed at which alteration of volume is occurring. There are two types of resistances to movement, one offered by the airways to the flow of gas and the other offered by the tissues to deformation. Generally, the two are measured together and are called total lung resistance. Measurement of these variables requires knowledge of the volume moved (spirogram), the rate at which this movement is occurring (pneumotachogram) and the pressure required to perform this work. The last, the average pleural pressure, can be recorded fairly accurately by intra-esophageal pressure measurements. From these variables the

total work of breathing can also be measured. Recent reviews of this subject are available (18, 27).

Such measurements permit correlation of the degree of breathlessness with objectively determined forces and resistances required for the act of breathing. The actual work performed by the respiratory muscles cannot be related to dyspnea because work involves both the force and the distance through which it acts. The greatly increased O_2 consumption of muscles struggling against a completely obstructed airway would involve practically no "work" because no change in distance (or volume) occurs. Therefore, it has been found better to relate dyspnea to the force acting on the lungs (23) or to the added O_2 consumption due to the respiratory work (10, 13).

Referring again to the tabulation above, the O_2 consumption required by the respiratory muscles, or the force which they have to exert, may be abnormally increased in two ways: this "work" may be greater than normal for a normal ventilatory requirement because the lungs, the thorax, or both, are abnormally uncompliant or the total lung resistance is increased (Group I); or compliance and resistance are not significantly altered but the total minute gas exchange for a given degree of activity may be greater than normal; here again the O_2 consumption of the respiratory muscles is abnormally increased in relation to the required performance (Group II). In this regard, breathing has been compared to walking, which is also a rhythmic, almost subconscious activity (14). A sensation of conscious muscular effort is likely to arise during walking either with decreased ability, as with a musculoskeletal impairment, or with increased demand, as on climbing a hill. As with dyspnea, the ratio of ability/demand at which a sensation of effort is first noted will depend upon psychologic awareness as much as upon physiologic stimuli.

Fortunately, a detailed analysis of the mechanics of breathing, such as that described above, is not required for clinical evaluation. A reduction in performance during voluntary maximal effort generally permits fairly accurate interpretation of the defective mechanics. Reduced compliance is generally associated with a reduction in the total vital capacity (VC).* This is because the

*See List of Abbreviations, following the text.

small or shrunken lung, the stiff, edematous lung or the small or deformed thoracic cage requires not only a greater force for a given amount of stretch but also maximal force to achieve a less than normal degree of stretch. Increased total lung resistance can manifest itself only while gas is being moved. Consequently, VC may be perfectly normal in the face of greatly increased resistance if enough time is allowed for the maneuver. Any measure of lung resistance must include an expression of rate of flow. The timed VC,* (maximal volume which can be moved during the first, first two and first three seconds of the maximal expiratory effort), the maximal midexpiratory flow rate and various measures of peak flow rate are all suitable measures for increased lung resistance. The volume of MBC in liters per minute depends on both the volume which can be moved with each breath and the speed with which this volume is moved. Therefore, it is reduced both by a diminution of the maximal stroke volume (decreased VC) and by an increase in the total lung resistance; it correlates better with dyspnea than the VC alone (Fig. 2). Thus far, it has been assumed that the maximal force which can be applied to the system, the strength of the respiratory muscles, is normal. Obviously, both VC and the various measures of flow rate are reduced if these muscles are malfunctioning or uncoordinated.

A detailed description of pulmonary function tests is not required for discussion of causes and treatment of dyspnea. However, because in clinical practice rational treatment of dyspnea is often impossible without a more or less comprehensive functional analysis, reference is made to several recent publications (2, 8, 11, 12, 17).

DECREASED BREATHING CAPACITY

Decreased Breathing Capacity Due to Restrictive Ventilatory Impairment

Diminution of the maximal stroke volume of the thoracic pump is reflected faithfully by diminution of VC. Ventilatory insufficiency of this type has been called "restrictive" (2) and occurs whenever *(1)* the compliance of the lungs, the thorax, or both,

*See List of Abbreviations, following the text.

is diminished or *(2)* the driving motor of the pump—the respiratory musculature—is impaired. The compliance of the lungs and thorax may be decreased by deformity of the thoracic cage (kyphoscoliosis, thoracoplasty), by encroachment upon the pleural space even if slight (pneumothorax, hydrothorax, cortex), by abdominal distention of great magnitude (severe ascites, severe gastric dilatation), by enlargement of the mediastinum (tumor or enlarged heart), by displacement of lung tissue from within (poorly ventilated cysts, tumor, pneumonia, edema) or, finally,

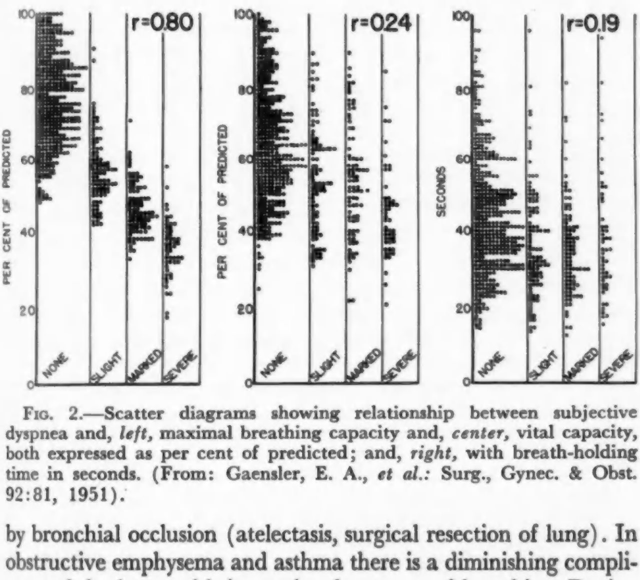

Fig. 2.—Scatter diagrams showing relationship between subjective dyspnea and, *left,* maximal breathing capacity and, *center,* vital capacity, both expressed as per cent of predicted; and, *right,* with breath-holding time in seconds. (From: Gaensler, E. A., *et al.:* Surg., Gynec. & Obst. 92:81, 1951).

by bronchial occlusion (atelectasis, surgical resection of lung). In obstructive emphysema and asthma there is a diminishing compliance of the lungs with increasing frequency of breathing. During static measurements, compliance is larger than normal (less elastic recoil), but during fast breathing, many partially obstructed lung regions no longer participate in ventilation and the patient actually breathes with a smaller lung.

In general, in restrictive ventilatory insufficiency the MBC is not as greatly impaired as the VC. There is usually little dyspnea

unless insufficiency is extreme or exercise severe. For example, after pneumonectomy, with one normal remaining lung the VC is always reduced to 50 or 60% of normal, yet the MBC is almost always above 65 and may be as high as 80% of normal. This is, in part, because the relative resistance of the upper airways is less for gas exchange of one lung and, in part, because of unusually regular and forceful respiratory maneuvers. Perhaps the constantly greater use of the respiratory musculature leads to improved coordination and muscular hypertrophy much like that which follows increased use and training of other groups of striated muscle. A VC which is one half of normal is compatible with a normal life and a great variety of sedentary occupations. Many of our pneumonectomy patients have had several normal pregnancies, and a number perform manual labor including locomotive and truck driving, assembly and custodial work.

The severest restrictive impairment is seen with bilateral pneumothorax or thickened pleura, in kyphoscoliosis, after resection of more than one lung and in severe pulmonary fibrosis. Even with a VC of 800–1,000 ml., patients tend to adapt their activity to their pulmonary reserve. Frequently, dyspnea is denied and, when questioned about their sensation on climbing one flight of stairs, these patients reply that, naturally, they never climb a flight all at once, so they do not know how they would feel! However, these patients live precariously because a restriction of the VC below 1,000 ml. leads to serious reduction of the pulmonary vascular bed. This is illustrated by the unhappy sequence of events in the following patient:

A. D., a 33-year-old housewife, was first admitted with extensive pulmonary tuberculosis at the age of 14. Although she improved after a left artificial pneumothorax, she soon developed a large right apical cavity with frequent hemoptysis and eventually required a right five-rib thoracoplasty. Because of persistently positive sputum and extensive cavitation throughout the left lung, a left pneumonectomy and space-confining thoracoplasty was performed which controlled her disease. She was discharged nine years after admission, apparently well, with a VC of 1,100 ml. (38%) and an MBC of 55 L./min. (60%) (Fig. 3).

She married, performed all of her household duties without difficulty, never complained of dyspnea and looked the picture of health. At 30 she became pregnant and had a normal term delivery without dyspnea

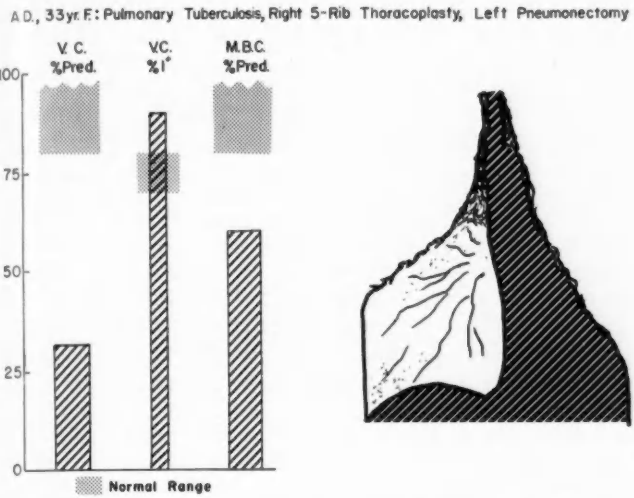

FIG. 3.—Dyspnea and acute cor pulmonale due to severe "restrictive" ventilatory impairment (right five-rib thoracoplasty and left pneumonectomy).

at any time. After a move to a bigger house with large grounds she became increasingly fatigued and complained of occasional substernal pain and "blackouts" when trying to catch up with her very active child. Her VC was then 920 ml., with 90% delivered in 1 second, and the arterial O_2 saturation was 96%.

One day, after "spring cleaning" and a prolonged pursuit of her child through nearby woods, she "blacked out" and on regaining consciousness felt very short of breath for the first time. That evening her ankles were swollen, she wheezed and had to sleep on three pillows for the first time. The second night she could sleep only in the sitting position and her lower legs and knees were now swollen. She was admitted with a diagnosis of acute cor pulmonale and died 2 hours later despite rapid digitalization, O_2, diuretics and other supportive measures. The only striking finding at postmortem examination was a hugely dilated right ventricle and a small amount of fluid in the right chest and peritoneum.

Chronic right heart failure not uncommonly coincides or even precedes the onset of "objectionable" dyspnea in patients with very severe restriction. A sequence of events similar to that observed in patient A. D. is often seen in middle-aged patients with kyphoscolios. Cardiorespiratory failure is usually precipitated by a minor respiratory infection, bronchopneumonia, unusual exertion or spontaneous pneumothorax.

Treatment.—The most important consideration concerning restrictive ventilatory impairment is prevention. Often after poliomyelitis or other palsies of childhood, attention is focused upon corrective measures for the legs to enable walking. Some years later, with good reconstruction and adequate braces, the patient may no longer be able to walk because of pulmonary insufficiency due to kyphoscoliosis. Spinal curvature and all pleural disease, especially empyema, should be treated promptly. Pleural effusions or traumatic hemothorax should suggest prompt aspiration because development of an "imprisoned lung" is unpredictable. Collapse or resection therapy for tuberculosis or bronchiectasis should not be performed if it will reduce the VC below 1,200 ml., regardless of any possible residual disease. Artificial pneumothorax, the worst offender in relation to restrictive insufficiency, fortunately has been largely abandoned.

Surgical correction for restriction of lung volume, when it is possible, should be used early before onset of right heart failure and before advancing age increases the operative risk. Dyspnea due to chronic restrictive disease can only get worse. Pulmonary decortication may be dramatically successful even after 10 or 20 years of collapse (28). The degree of functional restoration depends upon the severity of the initial parenchymal disease and upon bronchial integrity. Diaphragmatic eventrations should be reduced and repaired whenever possible. Lung cysts should be excised if they are symptomatic, increase in size or compress adjacent lung tissue, if function studies show a restrictive impairment or if there is marked asymmetry of function as demonstrated by split-function studies of the right and the left lung (bronchospirometry*).

*See List of Abbreviations, following the text.

A severe restrictive defect due to a space-occupying mediastinal lesion, and its surgical correction, is illustrated by the following case:

H. C., a 61-year-old inspector, had "always" had a cough productive of ½ oz. of greenish sputum. He had received compensation payments when a chest roentgenogram taken 25 years previously showed his "heart on the wrong side." Sixteen years ago he was admitted to a sanatorium, had 12 thoracenteses productive of "milk-like" material and was then told he did not have tuberculosis. About 2 years ago he first noted weakness, wheezing and progressive shortness of breath which eventually forced him to stop working. The chest roentgenogram revealed a huge mass in the left chest which almost completely obliterated the left lung field and caused a marked shift of the mediastinum (Fig. 4). Because of teeth within this mass, a diagnosis of benign mediastinal tumor was made and he was referred for study to decide whether his recent dyspnea was due to obstructive emphysema and asthma or to encroachment upon the lung by tumor. Also, he was to be evaluated as an operative risk.

Studies revealed a severe "restrictive" impairment with MBC one half of normal and VC of only 1,300 ml. There was no airway obstruction. Bronchospirometry revealed the left lung to be completely functionless (Fig. 4). Results suggested that this patient did not have obstructive emphysema, that he would be an adequate risk for left thoracotomy because there was no function on that side and that operation should improve function.

A huge mediastinal teratoma was resected. Dyspnea disappeared completely and the patient resumed work. Function studies showed disappearance of the restrictive defect. Repeated bronchospirograms revealed that not only had the left lung been restored to considerable function but the VC on the unoperated side had improved greatly as the result of return of the mediastinum to the midline (Fig. 4).

Chronic, compensated restrictive impairment need not cause great concern if the VC is greater than one half of normal and is fully exhaled in 2–3 seconds. With more severe impairment, long-term prognosis and hope of restoration to useful activity are not as good. Here, as in other conditions associated with pulmonary hypertension at rest, activity should be limited to the cardiopulmonary reserve. Any attempt to "practice" or to force progressive exercise usually has an adverse effect and may lead to syncopal attacks and acute right heart failure. The prevention of respira-

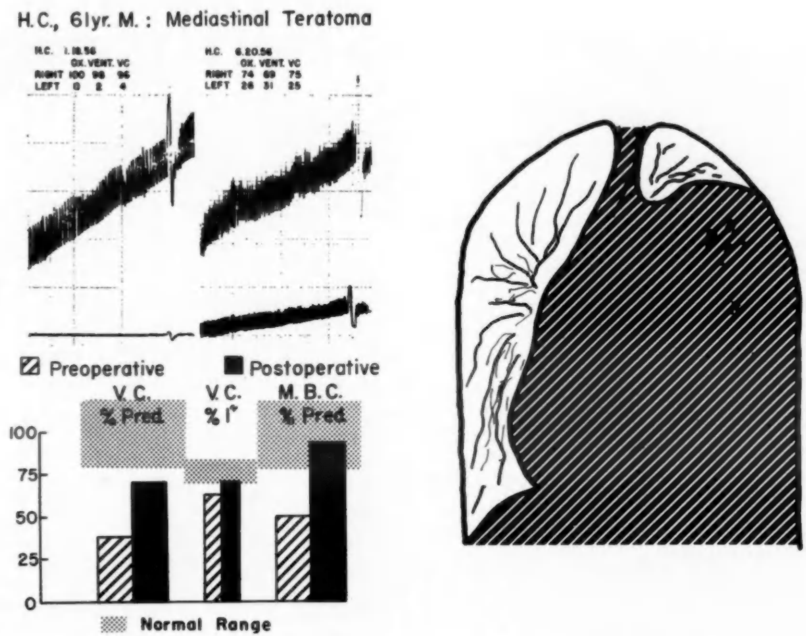

FIG. 4.—Progressive dyspnea due to severe "restrictive" ventilatory impairment (mediastinal teratoma) relieved by resection of the space-occupying lesion. In the bronchospirograms, the tracing for the right lung is uppermost.

tory infections is most important. Relative isolation during the winter months is advised. When infection does occur, it should be considered a serious illness and treated promptly.

Decompensated restrictive respiratory insufficiency should be treated by temporary tracheostomy before the patient is moribund. This has two major effects: *(1)* it reduces the anatomic dead space to about one-half and thus either *(a)* reduces the work of breathing for the same alveolar ventilation or *(b)* increases alveolar ventilation for the same work of breathing; and *(2)* it makes the lower respiratory tract more accessible for cleansing. Oxygen therapy is most effective by improving tissue oxygenation, particularly of the myocardium, by reducing pulmonary vascular resistance and by reducing to some extent the work of breathing. Furthermore, O_2 in this situation is not as likely to depress respiration as in obstructive disease. Artificial ventilation is also more likely to be successful than in obstructive disorders. All types of positive-pressure breathing (including negative pressure around the body by tank respirator!) should be used with caution when cardiac output seems impaired.

Right heart failure is treated in the usual manner with digitalis, diuretics and diet, although complete rest and O_2 therapy are perhaps the most effective means of reducing pulmonary arterial pressure and providing a chance for myocardial recovery.

RESPIRATORY MUSCULAR PARALYSIS is a "restrictive" ventilatory impairment only insofar as its severity is mirrored by decrease of VC. Lung compliance and resistance are not immediately affected. In a general hospital, weakness of the respiratory muscles is seen with poliomyelitis, dermatomyositis, chronic polymyositis, myasthenia gravis and acute porphyria. As stated before, the "dyspnea" associated with underventilation of this type may be quite different from ordinary shortness of breath. Patients may have difficulty in talking; air hunger may express itself primarily by restlessness and rhythmic motions of the head and chin which represent efforts to activate the accessory respiratory muscles. Rising pulse rate and blood pressure are often warning signs. Evidence of excessive work of breathing, so apparent in other types of cardiorespiratory failure, is, of course, absent.

Treatment.—Artificial ventilation is easier in patients with paralysis of the respiratory muscles than in those with any other

type of cardiorespiratory failure. The shape of the artificial respiratory curve, the inspiratory/expiratory ratio, the depth and rate are not critical as long as minute alveolar ventilation is adequate. This relative ease of artificial ventilation may create a new problem, that of overventilation. Artificial hyperventilation leads to chronic hypocapnia, respiratory alkalosis and possibly to psychotic episodes. The threshold of the respiratory center to pH and/or P_{CO_2}* is progressively lowered much as during "acclimatization" of normal man to high altitude. Eventually overbreathing becomes mandatory and weaning from the respirator is much more difficult.

Lack of effective cough can be overcome, in part, by postural drainage, suction and those attachments of respirators which produce intermittently a high expiratory pressure in feeble imitation of natural cough. Nevertheless every minor respiratory infection tends to become a crisis, and with more serious infection atelectasis often cannot be prevented even by bronchoscopy or tracheostomy. Regularly applied thoracopulmonic stretch is most useful not only to avoid atelectasis but also to prevent thoracic contractures and progressively decreasing compliance of the lungs and thorax. Air-swallowing may be an important cause of further restriction of lung volume and must be watched for.

The dyspnea and occasional air hunger of patients in a respirator may be due to fear of its malfunction. Eventually, psychologic factors due to constant confinement and dependence on the machine may become the main problem in spite of occupational therapy and other diversions. Therefore, early change from a tank respirator to chest- or abdominal-pressure devices, rocking beds or glossopharyngeal breathing may be most effective in lessening the fear of suffocation.

Early therapy of paralysis of the respiratory muscles is often complicated by palsy of other groups of muscles whose integrity is required for maintenance of a patent airway. Lingual, pharyngeal or vocal chord weakness may render artificial ventilation completely ineffective. Early tracheostomy then becomes mandatory.

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*See List of Abbreviations, following the text.

Decreased Breathing Capacity Due to Obstructive Ventilatory Impairment

Diminished ventilatory capacity due to increased airway resistance differs in nearly every respect from that due to restrictive impairment. In the latter, compliance is rarely decreased to less than one half of normal, whereas in obstructive impairment expiratory airway resistance may be 20–40 times normal. Obstruction is poorly tolerated and quickly leads to dyspnea from excessive work of breathing. The pressure drop required to produce a given rate of turbulent flow through a tube is inversely proportional to the fifth power of the diameter. Thus, a reduction to one half of the original diameter of a major airway theoretically may cause a 32-fold increase in the pressure required to produce the same rate of flow. This is borne out by clinical experience: relatively minor tracheal obstruction due to old tuberculous strictures, carcinoma of the thyroid or a too small tracheostomy tube may cause remarkable exertional dyspnea.

Expiratory resistance is increased by two peculiar circumstances which render an airway quite unlike a stiff metal tube: *(1)* the (intrathoracic) pressure applied to one end of the airway to make the gas flow is also applied outside to the entire length of the tube within the thorax, and *(2)* the airway is not rigid but rather is quite easily compressed. Bronchioles probably have no cartilaginous support, and in the larger bronchi this support is interrupted by the very flexible membranous portion. Thus, during expiration the pressure around the tube may become greater than the distal pressure within, with consequent "collapse" of the airway. Because of this, the usual relationship between pressure and flow rate may be lost: after a certain flow rate has been reached, it cannot be exceeded regardless of the pressure applied. In normal subjects this "critical flow" is very high, around 600 or 700 L./min., but in patients with intrinsic airway obstruction due to asthma or chronic obstructive emphysema, the maximal flow rate may become exceedingly low, 20 L./min. or less.

Hutchinson, who first conceived of VC, noted more than 100 years ago that certain patients with shortness of breath exhaled a normal volume on his spirometer. He ascribed this to a lack of "expiratory power." We now know that these patients did not

lack expiratory power but that airway obstruction greatly decreased the effectiveness of this power. The VC is quite useless in evaluating obstructive defects and therefore correlates poorly with dyspnea (Fig. 2); all significant functional measurements must relate volume to time. This is illustrated by the following case:

F. G., a 28-year-old laundress, was hospitalized for 2 years because of moderately advanced pulmonary tuberculosis. She responded well to bed rest, pneumoperitoneum and a 6 weeks' course of streptomycin (considered adequate at that time). She was discharged after a year and had worked ever since. However, dyspnea, first noted during the latter part of her stay at the sanatorium, slowly increased. More recently she had to "fight for her breath" even when walking a few steps; she noted gurgling noises in her chest, cough became ineffective and she felt that both air and secretions were "sticking in her throat."

The chest roentgenogram revealed only minimal apical scarring (Fig. 5). The total VC of 3.6 L. was normal, but she was able to exhale only 800 ml., or 25% of this volume in 1 second; and after 3 seconds barely one half of the VC was exhaled. Fluoroscopy showed severe, diffuse trapping of air with marked slowing of diaphragmatic and thoracic excursions. Bronchoscopy showed a severe stricture of the trachea about 2 cm. above the carina.

A portion of this strictured area was excised and about one third of the circumference of the trachea was replaced with a reinforced skin graft. Dyspnea disappeared completely. The total VC remained entirely unchanged but the volume she exhaled during the first second of this VC effort had increased from 800 to 2,800 ml. (Fig. 5).

Unfortunately, obstructive impairment is rarely due to simple, benign lesions of major airways. Most often this type of impairment is caused by diffuse obstruction throughout the lungs. In bronchial asthma this is thought to be caused by edema of the bronchial mucosa, increased tone of the bronchial musculature, or both. In chronic obstructive emphysema the obstruction may begin with bronchiolitis, an intrinsic weakness of smallest airways or an alteration of elastic tissue. This obstruction is then greatly aggravated by progressive disruption of the pulmonary architecture, decrease of "lung tension" and consequent lack of support for the smaller airways, which collapse during expiration because of the unfavorable extraluminal-intraluminal pressure relationship.

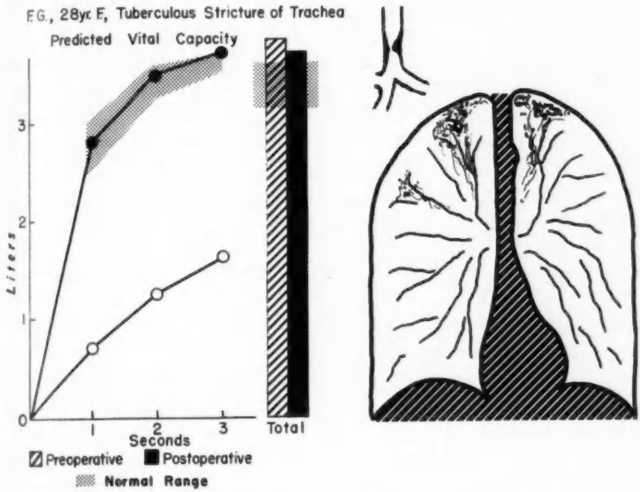

FIG. 5.—Dyspnea due to severe obstructive ventilatory impairment (tuberculous stricture of the trachea).

Chronic obstructive emphysema demonstrates best that dyspnea is usually caused by several factors. The various mechanisms which contribute to the total sensation of breathlessness in this disease are summarized in Figure 6. Dyspnea *(D)* initially is due largely to increased work of breathing as a result of increased airway resistance. Cough is relatively ineffective because rapid flow rates cannot be produced. The feeble, unproductive cough itself contributes to dyspnea and also is responsible, in part, for repeated, prolonged respiratory infections. Progressive parenchymal disruption with diminishing elastic recoil leads to increase of functional residual capacity (barrel chest); with this the insertion of inspiratory muscles becomes disadvantageous, further increasing the work of breathing. With increasing disruption of the lung there is increasing ventilation of poorly perfused alveoli. This leads to added dead space ventilation, which still further increases the work of breathing.

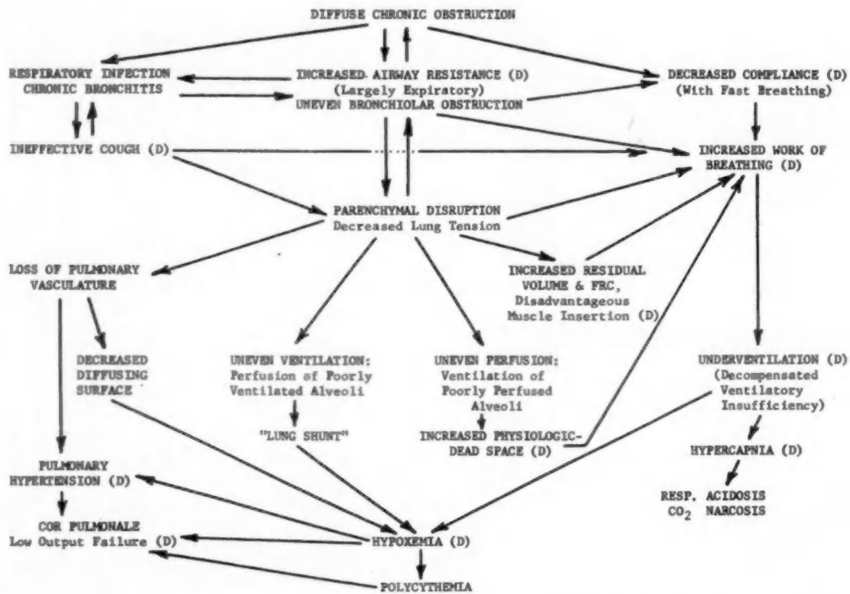

FIG. 6.—Cardiorespiratory abnormalities leading to dyspnea *(D)* in chronic obstructive emphysema.

Hypoxemia results from alveolar underventilation, a decreased diffusing surface and perfusion of poorly ventilated alveoli (lung shunt). Hypoxemia itself may contribute to dyspnea by excitation of the respiratory center via the chemoreceptors. Also, it impairs respiratory muscular activity and causes accumulation of metabolites at these sites, resulting in respiratory fatigue and dyspnea.

Increasing pulmonary vascular resistance comes not only from parenchymal disruption but also from hypoxemia. The right heart, already under stress, is at a great disadvantage when performing additional work under hypoxic conditions. Both the pulmonary hypertension and the ensuing low output failure again contribute to dyspnea.

Evidently, there is no aspect of pulmonary function and practically no factor enumerated in the classification given earlier which is not incriminated in the breathlessness of chronic obstructive emphysema.

Treatment of major airway obstruction.—Obstruction of a major airway is rare in comparison to diffuse obstruction. Surgical correction is performed whenever possible. It must be remembered that a relatively minor anatomic obstruction may cause severe dyspnea when rapid air flow is required. Any artificial airway with an internal diameter less than that of the trachea must add to the work of breathing. Oftentimes a too small tracheostomy tube is the sole cause of dyspnea while there is a frantic search for another cause of cardiopulmonary insufficiency. Finally, partial obstruction of major airways by adenoma, cylindroma, tuberculous stricture, mediastinal thyroid, etc., is often initially mistaken for bronchial asthma because both feature variable exertional dyspnea, evident increase in the work of expiration, wheezy breath sounds and often a normal chest x-ray.

Treatment of bronchial asthma need not be discussed here. Suffice it to say that often, particularly in elderly men, a strict separation and quantitation between asthma and emphysema is not possible. Almost all patients with chronic bronchitis and obstructive emphysema improve both objectively and subjectively on administration of bronchodilators. Such therapy should not be set aside even when it is evident that pulmonary dysfunction is due largely to irreversible pulmonary parenchymal changes.

Treatment of chronic obstructive emphysema.—A glance at Figure 6 suggests that treatment must be directed toward breaking of the vicious cycle of diffuse obstruction—increased work of breathing—parenchymal disruption—ineffective cough with inability to handle infection—further obstruction—further parenchymal disruption, and so on. The most effective point for attack is the chronic bronchitis and recurrent infection. Cigaret-smoking must be discontinued; this single measure is perhaps more useful than any other in arresting cough, improving pulmonary reserve and preventing further progression of the disease. Relative isolation during the winter months, avoidance of crowds and, ideally, a move to a warm, dry climate may all be effective in decreasing the number and severity of respiratory infections. Prompt, specific chemotherapy for infections is imperative, but prophylactic chemotherapy is not advised except in very special circumstances. Continuous, unproductive cough is undesirable both because it contributes to respiratory fatigue and because the forced inspiration preceding each cough with subsequent trapping of gas leads to further disruption of the lung. Sometimes it is possible to teach patients to cough less often but more effectively. Postural drainage is helpful in this regard. Expectorants are not often effective. Increased humidity facilitates the raising of tenacious secretions.

Dyspnea, and the increased work of breathing, can be attacked in other ways. Breathing exercises are recommended enthusiastically by some and are greatly valued, particularly in Scandinavia. We have had little success with this, perhaps because we have been poor instructors. The importance of bronchodilators, particularly by aerosol, and perhaps with the help of intermittent positive-pressure breathing (IPPB), has been mentioned. Abdominal belts may be tried and pneumoperitoneum is of significant help in about 10% of patients. In the rare obese patient, weight reduction is helpful in decreasing the work of breathing. Complicating hyperthyroidism may be overlooked in these very dyspneic, nervous patients. Its treatment again significantly reduced the ventilatory demand. Indeed, induction of hypothyroidism by radioiodine has been used in chronic obstructive emphysema to reduce metabolic rate, ventilatory demand and the work of breathing. It is important to teach patients to limit their activity to their pulmonary reserve. An increase of exercise or "training"

is to no avail; on the contrary, it aggravates pulmonary hypertension.

The treatment of pulmonary failure has been discussed recently in this publication (11). Initial therapy has two aims: increase of ventilation, and treatment of the factor which precipitated failure.

Artificial ventilation in decompensated obstructive insufficiency may present almost insurmountable problems. IPPB, which produces marked hyperventilation in normal subjects and in patients with lesser degrees of respiratory impairment, may fail because of the rigid breathing pattern. Changing of the rhythm, cycle and inspiratory-expiratory ratio in these patients with a fixed respiratory pattern, and the high end-inspiratory alveolar pressure imposed by most IPPB machines, may actually increase the work of breathing and lead to a further rise of P_{CO_2} with decreasing alveolar ventilation (20). Body respirators which are not patient-cycled and which impose a rigid breathing pattern are usually quite ineffective: spontaneous breathing efforts are not synchronized with the respirator, and again the work of breathing may be increased. Because of these problems, the suggestion has been made to ventilate these failing patients with automatic pumps following respiratory paralysis induced either by morphine or by muscle relaxants. Life then depends upon adequate intubation, the machine and the team of physicians and nurses. Therefore, this type of management has not received extensive trial. The advantages of a temporary tracheostomy in the treatment of respiratory failure have been mentioned.

The precipitating cause of respiratory failure is usually a respiratory infection, right heart failure or, occasionally, spontaneous pneumothorax. "Shotgun" broad-spectrum chemotherapy is essential because there is no time for analysis of the type and sensitivity of organisms. Treatment of cardiac failure by diuretics and digitalis is most effective if there is emphasis on treatment of the underlying pulmonary disease. Significant polycythemia is rare until the onset of cardiorespiratory failure. Slight polycythemia may be helpful by increasing the O_2 capacity of the blood. Phlebotomy, suggested largely to decrease blood viscosity to reduce pulmonary hypertension, is necessary only if the hematocrit is very high, 60% or more, or for the treatment of cardiac failure.

The dangers of O_2 therapy in obstructive respiratory failure have been greatly emphasized in recent years, so much so that it may not be amiss to emphasize again the important and specific benefits of O_2.

Hypoxemia has a great many detrimental effects (Fig. 6). It contributes to dyspnea by increased chemoreceptor drive and because of respiratory muscle malnutrition; it contributes to pulmonary hypertension and right heart failure by placing the heart under metabolic stress and by increasing pulmonary vascular tone, and it is the cause of increasing polycythemia. Severe hypoxemia may lead rapidly to irreparable central nervous system damage and, if uncorrected, to death in a few minutes.

All three basic causes of hypoxemia are corrected by O_2 therapy: *(1)* The effect of underventilation with its parallel increase of alveolar P_{CO_2} and decrease of alveolar P_{O_2} is, of course, corrected only as far as O_2 is concerned. *(2)* The effect of "lung shunts" due to perfusion of underventilated alveoli is largely corrected because, if the tracheal O_2 tension is raised from the normal 140 mm Hg to 300 or 400 mm, the O_2 tension within even very poorly ventilated alveoli will be raised at least to normal levels (a degree of "shunt" persists only because of perfused but completely unventilated alveoli). *(3)* The effect of a decreased diffusing capacity of the membrane is enhanced in this type of respiratory failure because the available pressure to drive O_2 across the membrane is low due to underventilation, quite unlike that seen in the "alveolar-capillary block" syndrome in which hyperventilation increases the O_2 pressure gradient. Here again O_2 breathing raises the mixed venous-alveolar pressure gradient so much that the diffusing impairment is nullified.

Certainly in the face of severe respiratory acidosis, sudden high O_2 breathing may lead to CO_2 narcosis because the now important chemoreceptor respiratory drive is abolished. Yet, there is some evidence that the loss of sensitivity of the respiratory center to the CO_2-pH stimulus may have been overestimated: failure of patients with emphysema to hyperventilate on CO_2 inhalation is at least in part due to high airway resistance and a mechanical inability to hyperventilate (3, 5). Although administration of O_2 is strongly indicated, it is important to initiate therapy with concentrations only slightly above 20% or with very low flow rates

and to increase only slowly. It is equally important to observe closely the frequency and depth of respiration. Suspected underventilation should be checked by repeated pH or P_{CO_2} measurements during initial therapy. The latter has been greatly facilitated by development of infra-red CO_2 analyzers (19).

DYSPNEA DUE TO INCREASED VENTILATORY DEMAND

In most patients with dyspnea, the complaint is caused by a significant reduction of breathing capacity. However, an abnormally large ventilatory demand alone may also lead to significant exertional dyspnea. In patients with cardiopulmonary disease, such an increased ventilatory demand often appears together with a decreased breathing capacity and thus contributes to dyspnea more significantly.

HYPERVENTILATION

A review of various factors contributing to cortical stimulation of hyperventilation has appeared recently in this publication (32). The following discussion is primarily concerned with hyperventilation of cardiopulmonary origin. There are two general types of hyperpnea: that which is due to an abnormally increased O_2 consumption (metabolically justified hyperventilation), and that which is out of proportion to O_2 uptake (metabolically unjustified hyperventilation). A normal subject requires about 2.5 L. of external ventilation for an O_2 uptake of 100 ml.; that is, the ventilation equivalent for O_2 (V_{EO_2})* is 2.5 L./100 ml. O_2. In certain situations of abnormally increased O_2 uptake, as with fever, hyperthyroidism, obesity or moderate exercise, ventilation increases in parallel fashion with O_2 uptake and the V_{EO_2} remains normal. When ventilation increases out of proportion to O_2 consumption, as at high altitudes or with various pulmonary fibroses, the V_{EO_2} may be greatly elevated to 5 or more L./100 c.c. Often, both types of hyperventilation occur together. In pulmonary disease, metabolism is frequently increased because of abnormally great work of the respiratory muscles, and there may be additional hyperventilation because of hypoxemia, added dead space and

*See List of Abbreviations, following the text.

other factors. During pregnancy, there is marked hyperventilation without an increase of O_2 uptake during the first trimester, perhaps due to respiratory stimulation by progesterone-like substances. Later, O_2 uptake progressively increases, and near term both ventilation and O_2 consumption are elevated to an almost equal degree.

The causes of *metabolically unjustified hyperventilation,* and indeed the abnormal control of respiration, have not been explored as much as other aspects of respiratory pathophysiology. However, there must be many different stimuli to hyperventilation, just as there are multiple factors which control normal respiration. Among the factors to be discussed here are *(1)* increased external ventilation with normal alveolar ventilation because of increased dead space, *(2)* hypoxemia, *(3)* reflexly stimulated hyperventilation, and *(4)* increased sensitivity of the respiratory center. Others listed in the classification given earlier are the various acidoses and the whole complex of supratentorially stimulated hyperventilation.

HYPERVENTILATION DUE TO INCREASED ANATOMIC DEAD SPACE VENTILATION.—The normal anatomic dead space contains about 150 ml., or approximately 1 ml./lb. of body weight. It changes little in pulmonary disease, and consequently an increase of its volume is not an important factor in the production of dyspnea. However, the anatomic dead space becomes increasingly important with shallow breathing. Normally, only a third or less of each tidal volume is expended for dead space flushing. With decreasing tidal volume, more and more effort goes toward dead space washout; if the tidal volume decreases to 150 ml. or less, nearly all of the work of breathing is devoted to pushing the dead space gas back and forth, and what little alveolar ventilation does occur is largely due to turbulence and diffusion. With very shallow, rapid breathing, external ventilation may be two or three times greater than normal, with a correspondingly increased work of breathing, yet actually there may be alveolar underventilation.

Treatment.—Efforts should be made to relieve the cause of shallow breathing. If this is due to severe chest pain, blocking of intercostal nerves may be effective. Occasionally, sedation may be indicated. Shallow breathing is one of several factors contributing to the dyspnea of pulmonary edema; in part, opiates are helpful

in relieving pain and anxiety and thus cause slower and deeper breathing. In other situations, for example, pulmonary embolism, virus or aspiration pneumonia and severe pulmonary fibrosis, the frequent, shallow breathing cannot be treated directly. Tracheostomy may then be of greatest value: if the tidal volume is 700 ml., a reduction of the anatomic dead space from 150 to 75 ml. has no significant effect on external ventilation and the work of breathing; however, if the tidal volume is only 150 ml., halving of the anatomic dead space may cause dramatic relief of dyspnea.

HYPERVENTILATION DUE TO INCREASED PHYSIOLOGIC DEAD SPACE.—Ventilation of alveoli which are not perfused with blood or, more commonly, are underperfused with respect to their ventilation, results in an effective additional dead space which, added to the anatomic dead space, is called the physiologic dead space. Normally, the physiologic and anatomic dead spaces are nearly the same. Extreme examples of increased physiologic dead space ventilation are pulmonary embolism or absence of one branch of the pulmonary artery. Here nearly one half of every tidal volume ventilates a lung which is a useless sac of air. The other lung, which accommodates the entire cardiac output, requires a normal alveolar ventilation of about 4 L./min. Inasmuch as it cannot be ventilated selectively, the useless lung has to be ventilated 4 L. as well, with the result that the work of breathing is almost doubled. The vasculature is irregularly compromised in many types of cardiopulmonary disease, and therefore increased physiologic dead space ventilation is a common cause of breathlessness. Figure 6 illustrates this factor in chronic obstructive emphysema.

Treatment.—Diffuse pulmonary vascular destruction, whether due to lung disruption, granuloma, fibrosis or bullous and cystic formations, is irreversible, and therefore specific therapy, as with the antituberculous drugs or steroids, is never completely effective in restoring function nor in relieving dyspnea. Again, tracheostomy may provide temporary relief from extreme dyspnea.

Only rarely is physiologic dead space ventilation due to a local vascular lesion (thrombosis, congenital absence or previous surgical ligation of a branch of the pulmonary artery), and then the disadvantages of the excessive dead space must be weighed carefully against the advantages of the presence of lung as a normal thoracic filling material before resection is considered (22).

HYPERVENTILATION DUE TO HYPOXEMIA

The confusion concerning the importance of a lowered arterial O_2 tension in stimulation of respiration via the chemoreceptors is due largely to citation of acute experiments which are not applicable to situations of chronic hypoxemia. It is often said that hypoxemia must be extremely severe before it has a notable effect on respiration: for example, normal subjects exposed to 15 or 12% O_2 show no appreciable change in the rate or volume of respiration. This is not for lack of chemoreceptor response but rather because the respiratory center is adjusted to a normal pH and P_{CO_2}; any sudden increase of chemoreceptor activity is quickly nullified by the more powerful pH-P_{CO_2} control mechanism. However, if this hypoxic drive continues for many hours or days, the constant drive to hyperventilation eventually leads to a readjustment of the respiratory center to a lower P_{CO_2}. After this "acclimatization" has occurred, hyperventilation and respiratory alkalosis may be quite marked even though the P_{O_2} is only moderately decreased. This mechanism also works in the opposite way: if a normal man acclimatized to high altitudes is given O_2 or is brought rapidly to sea level, hyperventilation persists for some days until the respiratory center has readjusted. Similarly, chronically hypoxemic patients continue to hyperventilate even while breathing pure oxygen; and respirator patients who have been chronically hyperventilated develop extreme air hunger when ventilation is reduced, even though their P_{CO_2} may be only 30 mm. Hg at the time.

HYPOXEMIA DUE TO IMPAIRED DIFFUSING CAPACITY OF THE LUNGS.—The earliest patients in whom a decreased diffusing capacity of the lungs (D_L)* was demonstrated had a syndrome called "alveolar-capillary block" (1). However, since then many other situations of impaired D_L have been recognized. D_L may be decreased because the size of the membrane is severely diminished without its actually being thickened (chronic obstructive emphysema, extensive resection), because the alveoli are partially blocked without marked alteration of the lung membrane (pulmonary alveolar proteinosis, pulmonary calcinosis) or because of vascular occlusions which decrease the effective size of the mem-

*See List of Abbreviations, following the text.

brane (mitral stenosis, multiple pulmonary emboli), and D_L may be reduced with entirely normal lungs when the intracapillary resistance to diffusion is increased (anemia).

"Alveolar-capillary block" may result from any diffuse pulmonary involvement but is most typically associated with the various pulmonary granulomatoses (miliary tuberculosis, sarcoidosis, beryllium disease, eosinophilic granuloma, farmer's lung) and all diffuse pulmonary fibroses (Hamman-Rich syndrome, fibroses resulting from radiation or virus pneumonia, silicosis, asbestosis). Whether the hyperventilation associated with this syndrome is chiefly due to increased reflexes from shrunken or stiff lungs or to hypoxemia is not clear. At any rate, it results in a reduced alveolar CO_2 tension and correspondingly elevated O_2 tension. Although hyperventilation increases the work of breathing and may cause dyspnea, it is a favorable protective mechanism because it increases the pressure gradient available for movement of O_2 across the impaired membrane. Indeed, hyperventilation may be so marked that O_2 saturation may be nearly normal in spite of severe impairment of D_L. This compensatory mechanism is most effective at rest but may fail during exercise, when there is less time for alveolar-capillary equilibration. The following patient may be cited as an example:

W. M., a 48-year-old Negro, was admitted with extreme dyspnea of 3 days' duration and temperature of 102 F. He was too breathless to talk, but he improved rapidly with O_2 therapy. He had worked as a woodcutter until 9 years before when he moved to Boston and obtained a job as a sandblaster in a small foundry where he had worked ever since with minimal protective devices. He had noted increasing exertional dyspnea for the past 9 months. Three days previously he became acutely ill with breathlessness, chills and fever. The chest roentgenogram showed very little radiolucent lung. He was treated for pneumonia. The temperature rapidly returned to normal and he could again breathe without O_2. However, exertional dyspnea persisted, and the x-ray film now showed diffuse granular haziness throughout both lungs and some heavy nodulation at the apex of the left lung.

Pulmonary function studies (Fig. 7) revealed an MBC of 125% of predicted, a VC which was only slightly reduced and a normal percentage exhaled in 1 second. Resting O_2 saturation was 91% and he hyperventilated markedly. During steady exercise, P_{CO_2} was only 30 mm. Hg and alveolar oxygen pressure (P_{AO_2}) was 115 mm. Hg

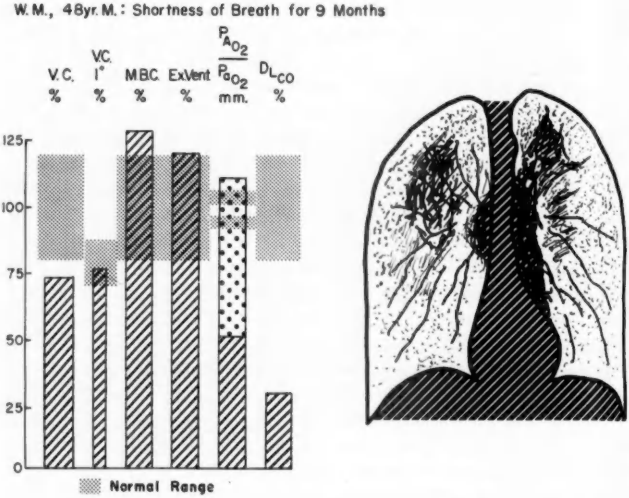

Fig. 7.—Dyspnea due to "alveolar-capillary block" syndrome with hypoxemia and alveolar hyperventilation (diffuse silicosis).

(normal, 105 mm.). Yet, arterial oxygen pressure (Pa_{O_2}) was only 52 mm. Hg and the alveolar-arterial P_{O_2} difference (A-a gradient), which normally should be no more than 10 mm. Hg, was 63 mm. Hg and the O_2 saturation was only 76%.

Hypoxemia in this case was not due to underventilation; on the contrary, it persisted in spite of overventilation. It could have been due to a marked shunt, to decreased D_L, or to both. D_L, measured by a carbon monoxide technique, was only 4.7 ml./min./mm. Hg, compared to a normal predicted of 20 ml. A lung biopsy confirmed the diagnosis of severe "alveolar-capillary block" due to silicosis. Usually, this disease leads to changes typical of chronic obstructive emphysema. Here a rather acute exposure over a short period led to changes which were more reminiscent of interstitial fibrosis and pneumonitis and resulted in a diffusion impairment. The usual tests of mechanics of breathing failed to give any indication of the pulmonary impairment nor did they offer a clue to the extreme exertional breathlessness of this man.

Treatment.—Hypoxemia resulting from "pure" alveolar-capillary block can be relieved completely by O_2 breathing. This raises the alveolar O_2 pressure, and consequently the alveolar-venous O_2 pressure difference, so greatly that the rate of diffusion is accelerated at least to the extent of causing complete saturation of the blood. Oxygen therapy here does not entail the dangers of CO_2 narcosis because the sensitivity of the respiratory center to CO_2 is increased rather than decreased. Impairment of diffusing capacity does not lead to CO_2 retention because the solubility of CO_2 in the pulmonary membrane is many times greater than that of O_2. Oxygen therapy is particularly important during intercurrent infections and in the postoperative period after lung biopsy, a frequently indicated intrathoracic procedure in these patients. When there is progressive deterioration, it is well to withhold O_2 therapy as long as possible because, once started, it is usually impossible to wean these patients from O_2. Conversely, a move to a higher altitude or flying even in pressurized airplanes should be discouraged because a decreased alveolar O_2 tension greatly aggravates the effects of impaired D_L. A sudden increase of dyspnea should always lead to the suspicion of spontaneous pneumothorax, a common complication of many diffuse pulmonary granulomatoses and fibroses, especially eosinophilic granuloma, pulmonary alveolar proteinosis and scleroderma.

The effects of steroids in diffuse pulmonary diseases are difficult to evaluate, in part, because nearly everybody feels better during steroid therapy and, in part, because in several of these diseases spontaneous remissions are so common that objective functional or radiologic improvement after administration of steroids is difficult to evaluate. For example, of 41 symptomatic patients with eosinophilic granuloma of the lung collected from the literature, 75% of the untreated patients improved spontaneously and 69% of those treated with steroids improved. In sarcoidosis, the tendency to spontaneous remissions or cure is well known. The improved outlook in beryllium disease has been attributed to long-term steroid therapy. However, the better survival during the past 10 years may be explained, in part, by the fact that all patients who developed their disease early after exposure and in severe form died before the advent of steroids, whereas those who developed the illness more recently were exposed many years ago

and have a much milder form of the disease. Some patients who were said to have "Hamman-Rich syndrome" improved following the administration of steroids, but, in fact, many of these patients had a much milder form of pulmonary fibrosis or interstitial pneumonitis than that described by Hamman and Rich. In some situations, particularly pulmonary alveolar proteinosis and pulmonary calcinosis, steroids appear to be contraindicated because they cause no improvement and may lead to fatal complicating infections, particularly with various fungi. If it is believed that in the granulomatous diseases administration of steroids will promote resolution of the process and prevent irreversible fibrosis, these drugs should be considered. However, the decision to initiate therapy should not be taken lightly, because it implies commitment to long-term therapy, added expense, the dangers of various side effects, and often marked deterioration when these drugs are withdrawn for one reason or another.

HYPOXEMIA DUE TO "LUNG SHUNTS."—Perfusion of alveoli which are not ventilated or, more commonly, underventilated with respect to their perfusion, results in unsaturation of the arterial blood due to venous admixture. In normal subjects, a degree of venous admixture is due to ventilation-perfusion imbalances and drainage of bronchial, thebesian and other veins into the greater circulation. This shunt amounts to no more than 6% of the cardiac output and causes an alveolar-arterial O_2 pressure gradient of no more than 10 mm. Hg. An extreme example of "lung shunt" is massive atelectasis of one lung. Immediately, one half of the right heart output then flows through lung which is not ventilated, resulting in severe venous admixture, marked hypoxemia, usually evident cyanosis and commonly dyspnea. The arterial O_2 pressure drops severely because one half of blood with a venous O_2 pressure of 20–50 mm. Hg is mixed with one half with O_2 pressure of 95 mm. Hg; the CO_2 pressure does not rise significantly because the venous-arterial CO_2 pressure difference is only 6 mm. Hg and because minimal hyperventilation of the good lung compensates easily for any small rise which might occur. Blood flow through the atelectatic lung immediately decreases slightly because of increased vascular resistance partly caused by local hypoxemia in the lung and partly because the size of the lung is diminished by shift of surrounding structures.

However, some blood continues to flow through such a lung for many weeks or even months. Much more commonly, increased venous admixture results from relative underventilation of relatively well perfused lung regions. This mechanism in chronic obstructive emphysema is illustrated in Figure 6.

Treatment.—Oxygen therapy has little effect if hypoxemia is due to perfusion of entirely unventilated or atelectatic lung, much as it has no effect on cyanosis caused by congenital cardiovascular anomalies. However, oxygenation is improved when increased venous admixture is due to relatively underventilated areas.

The importance of prompt treatment of atelectasis needs no emphasis. The longer it persists the more difficult re-aeration becomes because surface tension forces increasingly tend to perpetuate collapse. Also, atelectasis, particularly that due to foreign bodies and that occurring postoperatively, is likely to lead to infection. Omission of sedatives and hypnotics, mobilization, encouragement to cough and use of expectorants may be helpful. The most effective treatment is repeated endotracheal suction, which not only permits removal of secretions but also prompts violent, spontaneous cough despite chest pain or lethargy. Bronchoscopy is indicated if a foreign body or organic lesion is suspected but otherwise, because of the incident trauma, is less desirable than catheterization, which can be performed much more frequently. Relative underventilation of well perfused alveoli is treated by all conventional measures which assist respiration. IPPB particularly has been shown to decrease the amount of venous admixture due to this cause.

Pulmonary arteriovenous fistula, a rare cause of venous-arterial lung shunt, requires excision if the lesion is shown to be single or localized.

Reflexly stimulated hyperventilation.—The contribution of reflexes to the total control of respiration has not been fully explored. The considerable preoccupation with the chemical control of respiration has tended to de-emphasize the importance of these reflexes. In normal man, it is thought that reflexes from the limbs, lungs, thorax, great vessels and probably other cites contribute significantly to the hyperpnea of muscular exercise (7). The role of such reflexes in the hyperpnea of cardiopulmonary disease is almost entirely conjectural. The dyspnea which

accompanies congestive heart failure has been thought to be due in large part to pulmonary reflexes as a result of an increased amount of blood in the lungs (6, 21, 34). Unfortunately, hyperventilation in cardiopulmonary disease occurs almost invariably in the presence of a number of abnormalities, both mechanical and chemical. Of these, all are more easily identified than reflex stimulation, and the latter is recognized as a cause of hyperventilation largely by exclusion. Occasionally, it is possible to identify pulmonary reflexes as the cause of hyperventilation, as illustrated by the following case:

B. S., a 57-year-old housewife, had a right radical mastectomy for carcinoma 4 years before we saw her. Surgery was followed by extensive axillary, chest and mediastinal irradiation totaling about 5,000 r. She did very well for 2 years, then noted increasing dyspnea which progressed so rapidly that she now complained even while walking slowly on the level. Physical examination revealed a stiff, brawny, indurated and immovable right hemithorax. The chest roentgenogram showed marked deviation of the mediastinal structures to the right, and the lung field was almost completely opacified by fibrosis, mediastinal shift and diaphragmatic elevation (Fig. 8). A bronchogram showed saccular deformation throughout the right lung.

Pulmonary function studies revealed an MBC which was 80% of the predicted normal and a VC of 55%, without undue delay. These studies were quite like those of patients after pneumonectomy with a normal remaining lung. Severe dyspnea could not be explained until ventilation measurements were made: the patient breathed about 100% more for a given O_2 uptake than a normal individual both at rest and during exercise. Her Pa_{CO_2} was reduced almost to 50% of the normal value (Fig. 8). Bronchospirometry showed that the right lung was practically functionless in that it contributed only 2% to the total O_2 uptake and 5% to the total ventilation, thus ruling out excessive physiologic dead space as the cause of dyspnea. Arterial O_2 saturation was 96% and P_{O_2} was normal, thus excluding hypoxemia as a cause of hyperpnea. The steady, unremitting nature of her hyperventilation and the equal severity of hypernea at rest and during exercise appeared to exclude a hyperventilation syndrome. Therefore, it was thought that this small, shrunken, fibrotic right lung destroyed by x-radiation was responsible for reflexes which excessively stimulated the respiratory center. Excision of this functionless right lung was therefore recommended.

The patient returned for function studies 3 months after operation. Dyspnea had almost completely disappeared and now she was able to climb two flights of stairs without difficulty. The MBC was unchanged and the VC was a few milliliters less than before operation. However, the ventilatory requirement both at rest and during exercise was now within the normal range, as was the P_{CO_2} (Fig. 8).

When reflex hyperventilation is suspected, a slight depression of the respiratory center by sedatives or narcotics may provide

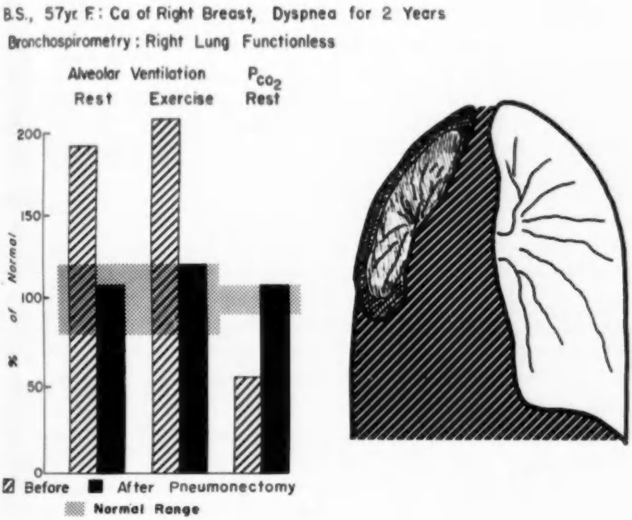

FIG. 8.—Dyspnea due to severe hyperventilation apparently stimulated by overactive lung reflexes (radiation fibrosis), relieved by right pneumonectomy.

considerable relief from dyspnea; this must be tried with great caution. The beneficial effect of narcotics in some forms of cardiac failure, particularly with pulmonary edema, is probably largely on this basis. Surgical extirpation for presumed excessive lung reflexes obviously is possible only in the rarest of instances.

DYSPNEA NOT ASSOCIATED WITH INCREASED WORK OF BREATHING.—A number of causes of breathlessness are listed under this heading in the classification given earlier. All of them, including respiratory muscle insufficiency, circulatory failure and decreased O_2 capacity of the blood, have tissue hypoxia as a common factor. The breathlessness in these conditions is probably due largely to respiratory muscle fatigue. In respiratory muscle insufficiency, immobility of the chest wall and imbalance between inspiratory and expiratory reflex stimuli probably contribute to the total sensation of dyspnea.

In certain situations, dyspnea is a common complaint, yet the mechanism of its production is poorly understood. Breathlessness is an early and important complaint in pulmonary hypertension. Usually this is explained on the basis of a low, fixed cardiac output; but some such patients with an output well maintained even during exercise have dyspnea as a prominent complaint. A number of situations of dyspnea with a poorly understood origin were mentioned in the section on experimental work.

Finally, there is a small group of patients who complain of shortness of breath in whom no evidence of organic impairment or of hyperventilation can be found. Very rarely, dyspnea may be complained of solely to achieve disability payments or some other monetary gain. Among some 4,000 patients whom we have seen in our laboratories during the past 14 years, there were no more than two or possibly three who clearly fell in this category. At times, there may be organic impairment which has not been detected. At times, problems of communication may lead to a misunderstanding between patient and physician. Occasionally, a complaint of dyspnea may be the result of faulty judgment by the patient, as illustrated by the following case:

M. P., a 64-year-old professor of geology, was referred because of increasing shortness of breath of 4 years' duration. Lung function studies were carried out first, because the referring physician's letter was not expected until later. The VC and the MBC were both above the average predicted normal for an individual of his stature and age (Fig. 9). Residual volume and intrapulmonary distribution of gas were normal. There was no hyperventilation at rest or during exercise. Because of these normal findings, arterial blood studies were performed during severe exercise walking on a treadmill at the rate of 5 mph on an 8%

incline. The patient was able to continue this exercise for 15 minutes without difficulty. Alveolar and arterial Po_2 were entirely normal and the "A-a gradient" was only 8 mm. Hg (Fig. 9). The diffusing capacity of 46 ml./min./mm. Hg was within the normal range, although not many of our normal control subjects in the past had been able to walk steadily at this rate and incline.

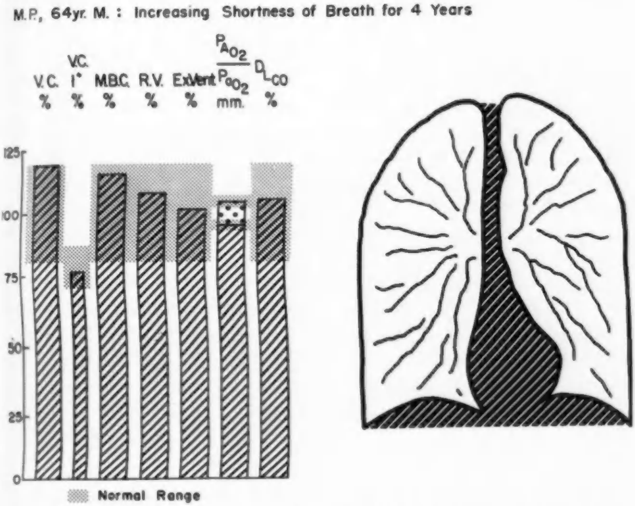

FIG. 9.—Dyspnea without impairment of breathing capacity, without hyperventilation and, presumably, without organic disease, apparently due to patient's failure to accept or recognize normal functional limitations associated with advancing age.

During a later interview the patient mentioned that his favorite pastime is mountain climbing and that only 7 years before, at the age of 57, he had participated in a major expedition to Mount McKinley. However, during recent years he had slowed down a little. During the past 2 or 3 years he climbed Mount Washington most weekends. He still reached the top ahead of others in the party, but when he arrived he was concerned to note that he was breathing quite hard! This 64-year-old man apparently had not considered the possible effects of advancing age; and his physician, who was aware of this, had referred him mainly to provide objective reassurance for this man.

CARDIAC AND PULMONARY DYSPNEA

It is hoped that this discussion of dyspnea has already suggested to the reader that the immediate mechanisms responsible for the production of dyspnea are the same in cardiac and in pulmonary disease. Dyspnea of cardiac origin, much like that of pulmonary origin, can be explained on the basis of decreased breathing capacity, increased breathing requirement, respiratory muscle fatigue or, usually, a combination of these factors. Indeed, mechanical factors in the lung were incriminated in the dyspnea of patients with cardiac disease more than 40 years ago (29).

Decreased breathing capacity may result from increased airway resistance. This event has been well documented in patients with mitral stenosis and may occur with either interstitial or overt pulmonary edema (4, 24). The term "cardiac asthma" is a clinical interpretation of this finding. The work of breathing also may be increased because the lung is less easily deformed: central venous congestion, increased blood in the lungs, interstitial fluid or frank edema, cardiomegaly, hepatomegaly, ascites and pleural effusion all may lead to a marked decrease of lung compliance (16, 23, 24). Certain anatomic changes resulting from chronic left auricular hypertension (Parker-Weiss changes* may also contribute to increased rigidity. Indeed, repeated VC measurements have been used for 60 years to follow the course of cardiac failure.

An increased ventilatory demand may result from excessive dead space ventilation due to rapid, shallow breathing. Further, the physiologic dead space may be markedly increased. In pulmonary edema particularly, there are marked ventilation-perfusion imbalances. Hypoxemia is not a prominent feature of acquired cardiac disease. The "cyanosis" of cardiac failure or pulmonary edema is often the result of what used to be called "stagnant anoxia," which presumably means a very low venous O_2 tension. However, slight hypoxemia is not uncommon in advanced heart disease and probably results largely from ventilation-perfusion discrepancies. A degree of "alveolar-capillary block" is a prominent feature particularly in conditions associated with

*Parker, F., Jr., and Weiss, S.: The nature and significance of the structural changes in the lungs of mitral stenosis, Am. J. Path. 12:573, 1936.

an abnormally elevated left auricular pressure and may contribute to hypoxemia and hyperpnea. Hyperventilation stimulated by pulmonary reflexes is said to be particularly prominent in pulmonary disease secondary to heart disease (21, 34).

Pulmonary hypertension resulting from elevated "back-pressure" is a further contributor to breathlessness. Low cardiac output, respiratory and other muscular fatigue are among the most important factors in the exertional discomfort of the cardiac patient and the reason why "dyspnea" occurs at a lower ratio of ventilatory demand/ventilatory capacity than in primary pulmonary disease (Fig. 1).

List of Abbreviations

Abbreviations have been avoided as much as possible. However, when used, they follow a generally accepted terminology (Standardization of definitions and symbols in respiratory physiology, J. R. Pappenheimer, Chairman, Fed. Proc. 9:602, 1950).

The total lung capacity (TLC) is composed of the vital capacity (VC) and the residual volume (RV), the volume remaining in the lungs after maximal forced expiration. The timed vital capacity (TVC), as used here, refers to the percentage of the total VC which is exhaled during a specified time interval from the beginning of the maximal expiratory effort. During the first second (1"TVC), normal individuals can exhale at least 75% of the total VC. Statement of this percentage is meaningless unless the volume of the total VC is also mentioned.

Maximal breathing capacity (MBC) is the volume in liters per minute which can be exchanged by maximal voluntary effort. Patients are instructed to breathe "as hard and fast as possible," and no effort is made to control the respiratory rate. The "dyspnea index" is the percentage of MBC required at rest or during a stated activity. "Breathing reserve" is the reciprocal of the dyspnea index—the percentage of MBC "left over," "not used" or "in reserve" at rest or during a stated activity.

The ventilation equivalent for oxygen (V_{EO_2}) expresses the external ventilatory requirement for a given oxygen uptake. Normally, this is 2.5 liters of ventilation per 100 ml. O_2 (or 25 L./L. O_2).

The partial pressure or tension exerted by a gas is abbreviated as P; the alveolar gas phase is denoted by a small capital A, and the arterial blood phase by a lower case a. Thus, alveolar oxygen tension becomes

P_{AO_2}, and arterial carbon dioxide pressure Pa_{CO_2}; the oxygen pressure difference between alveolar gas and arterial blood is usually referred to as the "A-a oxygen gradient."

The diffusing capacity of the lungs is termed D_L. Reference must be made to the gas which is being measured, either D_{LO_2} or D_{LCO}. D_L is defined as the amount of gas which crosses the alveolar-capillary membrane per unit of time per unit of pressure difference between the mean alveolar tension and the mean pulmonary capillary tension of that gas. The normal resting D_{LO_2} or D_{LCO} is between 12 and 25 ml./min./mm. Hg.

Bronchospirometry refers to a procedure involving intubation of the trachea and the left main bronchus with a double-lumen catheter, usually under topical anesthesia. Inflation of two balloons within the tracheobronchial tree permits isolation of the air passages of the left and right lungs and thus separate and simultaneous spirography for each lung. The normal right lung contributes approximately 55% to the total oxygen uptake, ventilation and vital capacity and receives approximately 55% of the total cardiac output. The left lung, of course, contributes approximately 45%.

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